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Similar effects of long-term exogenous growth hormone (GH) on bone and muscle parameters: A pQCT study of GH-deficient and small-for-gestational-age (SGA) children

Roland Schweizer [a], David D. Martin [a], Martin Haase [a], Johannes Roth [b], Branko Trebar [a], Gerhard Binder [a], C. Philipp Schwarze [a], Michael B. Ranke [a,*]

[a] *Paediatric Endocrinology Section, University Children's Hospital, Hoppe Seyler Strasse 1, D-72076 Tübingen, Germany*
[b] *Paediatric Rheumatology, Charité, Berlin, Germany*

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Abstract

Background and aims: Treatment with GH in short children has focused on height development. Little is known about the concomitant changes in muscle mass, bone structure and bone strength.
Methods: Muscle area as well as parameters of bone architecture (bone mineral content, BMC; volumetric cortical density, total bone area, TBA; cortical area, cortical thickness, CT; and marrow area) were measured by means of pQCT (Stratec) at 65% of the proximal length of the forearm. The strength–strain index (SSI) was calculated as an indicator of bone strength.
Results: Prepubertal children with GHD (mean values: age; 7.2 years; height SDS = −2.9 SDS; GH dose: 30 μg/kg/d) were followed at 0, 6, 12 (n = 74) and 24 (n = 55) months. Prepubertal children with SGA (mean values: age: 7.1 years; height SDS = −3.4 SDS; GH dose: 55 μg/kg/d) were followed at 0, 6, 12 (n = 47) and 24 (n = 35) months. Both groups showed a similar increase in height. At GH start, muscle mass and bone characteristics were lower than normal but similar in SGA vs. GHD. Muscle area (mean values, SDS) increased from −3.0 to −1.5 in SGA and from −2.4 to −1.0 in GHD. Bone geometry changed in a biphasic mode, with an increase in total bone area and lowering of bone mineral content (BMC) during the first 12 months, followed by an increase of BMC and CT thereafter. SSI (mean values, mm^3) improved from 78 to 114 in GHD and from 62 to 101 in SGA after 24 months on GH. The increment in terms of SDS did not reach significance in SGA. SSI correlated positively with muscle area before and during GH treatment.
Conclusions: Bone strength and muscle mass are impaired in prepubertal children with GHD and SGA. Exogenous GH can indirectly improve bone structure and strength by inducing an increase in muscle mass. Our findings support the assumption that, in SGA, there is impaired tissue responsiveness to GH.

Keywords: Strength–strain index (SSI); Bone strength; Muscle mass; Growth hormone treatment; Small for gestational age; Growth hormone deficiency; Bone mineral density

Introduction

As an indicator of bone health, bone strength takes precedence over bone mass. Recent studies by Hasegawa et al. [1] and Schönau et al. [2] illustrated that the strength of a bone is not only a function of its density but mainly of its geometry (i.e. cortical thickness and bone diameter). Thus, bone strength is determined by material characteristics, including mass, bone mineral content (BMC) and geometry, as well as the three-dimensional organization of the trabecules. Several studies have reported low bone mineral density (BMD) in adults and children with growth hormone deficiency (GHD) [3–6]. Some studies have reported a higher risk of fracture in adults with GHD [7,8]. There is little information available about bone and the effect of GH in short children born small for gestational age (SGA) [9]. The aim of our study was therefore to analyze bone

* Corresponding author. Fax: +49 7071 29 4157.
E-mail address: Michael.Ranke@med.uni-tuebingen.de (M.B. Ranke).

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structure and bone strength parameters in relation to muscle during GH treatment in children with GHD and short children born SGA.

Patients

Before and during treatment with recombinant human growth hormone (rhGH) of various brands, children followed at our Paediatric Endocrinology Section are subjected to a structured investigation including clinical examinations, anthropometrical measurements, fasting blood sampling and measurements of bone density, mass and structure (e.g. using DEXA or pQCT). These investigations are conducted at the start of GH and at intervals of 6, 12 and 24 months. The present study was approved by the independent ethics committee of the medical faculty of the University of Tuebingen and informed, written consent was given by the parents. The data we analyzed were collected from March 1999 to May 2005. Within this time span, 151 prepubertal children (47 girls) were followed for 1 year. In 121 children (GHD, $n=74$; SGA, $n=47$), a longitudinal data set (0, 6, 12 months) was available and the children were still prepubertal at the end of this time period. There were 30 children who were excluded for the following reasons: 7 GHD and 4 SGA patients started puberty during the first year on GH, 10 other patients had acquired GHD; 9 SGA patients were also GH deficient and did not meet the criteria. Similarly, in 90 children (GHD, $n=55$; SGA, $n=35$), a longitudinal data set (0, 6, 12 and 24 months) was available and the children were still prepubertal at the end of this time period. GHD was defined as follows: height for age <-2.0 SDS; peak GH to GH tests <8 μg/L [10]; serum IGF-I levels for age <-1.0 SDS; height velocity for age <0.0 SDS. SGA was defined as follows: height for age <-2.0; weight and/or length at birth <-2.0 SDS for gestational age; peak GH to GH tests >8 μg/L; height velocity for age <0.0 SDS. Patients with syndromes were excluded from the analysis, with the exception of those with Silver Russell syndrome.

Methods

The normal height standards of Prader et al. [11] were applied. For birth weight and birth length, the standards of Niklasson et al. [12] were used. The target height was calculated according to the method described by Tanner et al. [13]. Growth hormone levels were measured by in-house RIA as published [14] and IGF-I levels were compared to published references [15].

Bone mass, geometry and strength of radius of the non-dominant forearm were measured as described previously [16] by means of peripheral quantitative computed tomography (pQCT) using the XCT 2000 (Stratec, Inc., Pforzheim, Germany). The proximal radius of the non-dominant arm was chosen and cross-sectional measurements were taken at exactly 65% of the ulna length away from the forearm growth plate. For this, the forearm growth plate was precisely located with a scout-view scan. This position of measurement was chosen because it is the site comprising the biggest muscle area cross-section for which Schoenau at al. [17] established age-dependent reference values in 2001 using the same pQCT device for healthy German children. A relative (65%) distance was chosen because the arm grows continually during childhood. The following parameters were measured or calculated: cortical bone mineral content (BMC) [mg/mm], volumetric cortical bone mineral density (vBMD or cortical density) [mg/cm^3], total bone area [mm^2], cortical bone area (or cortical area) [mm^2], cortical bone thickness (or cortical thickness) [mm], marrow area (total bone area minus cortical bone area) [mm^2], the entire forearm and muscle area [mm^2]. To establish the variability of the measurements, 3 investigators measured the forearm of an adult volunteer 12 times. The coefficients of variation for total area, cortical area, marrow area, cortical thickness, cortical density and muscle area were 2%, 0.9%, 6%, 1.6%, 0.3% and 3%, respectively.

The strength–strain index (SSI) used for assessing bone strength of the forearm was described by Schönau et al. [2]. The formula for calculation of the SSI is SSI$=\Sigma(r^2\times a)\times(\mathrm{CD}/\mathrm{ND})/r_m$ [mm^3], with Σ being the sum; r, the distance between a voxel and the centre of gravity; r_m, the maximum distance of a voxel to the centre of gravity; a, the voxel area (0.4 mm × 0.4 mm = 0.16 mm^2); CD, the volumetric bone mineral density of a voxel; and ND, the maximum mineral density of human bone (1200 mg/cm^3) [18]. To assess the SSI of the forearm, we applied a threshold of 480 mg/cm^3 as per the default settings of the manufacturer's software. This choice of threshold is based on technical considerations pertaining to the partial volume effect, which is a source of error in QCT [19]. The partial volume effect refers to measurement errors caused by voxels that are only partially filled with mineralized bone. In the SSI analysis, the partial volume effect plays a minor role, owing to the fact that the individual density reading of each voxel is used for the calculation. All other bone parameters were measured at a threshold of 710 mg/cm^3. Tissue at a threshold between 30 and 70 mg/cm^3 was taken to be muscle.

Table 1
Basal characteristics of children with GHD ($n=74$) and short children born SGA ($n=47$)

		GHD ($n=74$), mean (SD)	SGA ($n=47$), mean (SD)	GHD vs. Norm (p)	SGA vs. Norm (p)	GHD vs. SGA (p)
At GH start						
Gestational age	[weeks]	39.38 (2.26)	36.16 (3.96)	n.s.	**	***
Birth weight	[SDS]	−0.18 (1.11)	−2.62 (0.91)	n.s.	**	***
Birth length	[SDS]	−0.39 (1.62)	−3.30 (1.33)	n.s.	**	***
Target height	[SDS]	−0.46 (0.73)	−0.56 (0.85)	**	**	n.s.
Max. GH in test	[μg/L]	5.34 (1.70)	12.95 (4.57)	**	n.s.	***
Age	[years]	7.19 (2.91)	7.07 (2.48)			n.s.
Height	[SDS]	−2.89 (0.58)	−3.41 (0.79)	**	**	***
HV before GH	[cm/year]	5.00 (1.38)	5.22 (1.67)	**	**	n.s.
GH dose	[μg/kg/d]	30.03 (3.73)	55.05 (10.24)			***
During GH						
HV 1st year	[cm/year]	9.31 (1.78)	9.20 (1.54)	***	***	n.s.
Δ Height 1st year	[SDS]	0.88 (0.42)	0.91 (0.37)	***	***	n.s.
HV 2nd year	[cm/year]	7.47 (1.29)	7.55 (1.21)	**	**	n.s.
Δ Height 2nd year	[SDS]	0.42 (0.32)	0.47 (0.28)	**	**	n.s.

n.s. = not significant; **$p<0.01$; ***$p<0.001$.